It's All Relative: A Validation of Radiation Quality Comparison Metrics

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Background

The difference between high-LET and low-LET radiation is quantified by a measure called relative biological effectiveness (RBE). RBE is defined as the ratio of the dose of a reference radiation to that of a test radiation to achieve the same effect level, and thus, is described either as an iso-effect or dose-to-dose ratio. A single dose point is not sufficient to calculate an RBE value; therefore, studies with only one dose point usually calculate an effect-to-effect ratio [1-3]. While not formally used in radiation protection, these iso-dose values may still be informative. Shuryak, et al 2017 [4] investigated the use of an iso-dose metric termed "radiation effects ratio" (RER) and used both RBE and RER to estimate high-LET risks.

To apply RBE or RER to risk prediction, the selected metric must be uniquely defined. That is, the calculated value must be consistent within a model given a constant set of constraints and assumptions, regardless of how effects are defined using statistical transformations from raw endpoint data. We first test the RBE and the RER to determine whether they are uniquely defined using transformations applied to raw data. Then, we test whether both metrics can predict heavy ion response data after simulated effect size scaling between human populations or when converting animal to human endpoints.

Data Collection

Models for Harderian gland tumor induction after gamma ray and heavy ion exposures were generated using mouse data from Chang, et al 2016 [5]. CB6F1/Hsd mice were irradiated acutely with ≤0.5 Gy of 260 MeV/u ^{28}Si or ^{137}Cs gamma rays. After 16 months, the number of animals with Harderian gland tumors (T) and the total number of animals alive at the end of this period (N) were recorded. Only animals alive at the end of the 16-month period were included in the analysis.

Methods: Study 1

Harderian gland tumor count (T) per number at risk (N) was analyzed as a binomial parameter. Two transformations of this binomial parameter were applied using the identity and log-complement link functions of generalized linear models (GLMs). To visualize the results from each GLM, we considered two different "effect scales" for the y-axis: tumor prevalence (T/N) and log tumor-free survival prevalence (ln[1-T/N]). The identity link has a linear relationship with the tumor prevalence effect scale, and the log-complement link has a linear relationship with the log tumor-free survival prevalence scale. Control data was analyzed using each link function prior to radiation modeling. Baseline tumor prevalence (c_{id}) was estimated using the identity link function, and baseline log tumor-free survival prevalence (c_{logc}) was estimated using the log-complement link function. Note that c_{id} and c_{logc} are transformations of one another: $c_{id} = 1\text{-}\exp(c_{logc})$

For each link function, Si and gamma ray data were analyzed in one GLM with radiation type as a categorical variable. The estimate for the appropriate control (i.e., c_{id} or c_{logc}) was modeled as a fixed parameter to force the y-intercept to be the observed background number of tumors. For both the identity and log-complement link functions, estimates of the linear slope with respect to dose were defined for each ion ($\alpha_{I,id}$ and $\alpha_{I,logc}$, respectively) and for gamma rays ($\alpha_{\gamma,id}$ and $\alpha_{\gamma,logc}$, respectively). Table 1 shows the relationship between link functions and effect scales with regard to effect estimates as a function of dose, E(D).

Since all our models can be simplified to a linear equation, the RBE is:

Equation 1: $RBE = \frac{\alpha_I}{\alpha_\gamma}$

The equation defined in Shuryak, et al 2017 [4] is used to calculate the RER:

Equation 2: $RER = \frac{E_I(D) - E_I(0)}{E_\gamma(D) - E_\gamma(0)}$

The equations from **Table 1** can be placed in the RER formula to calculate the resulting RER values when different link functions and effect scales are selected.

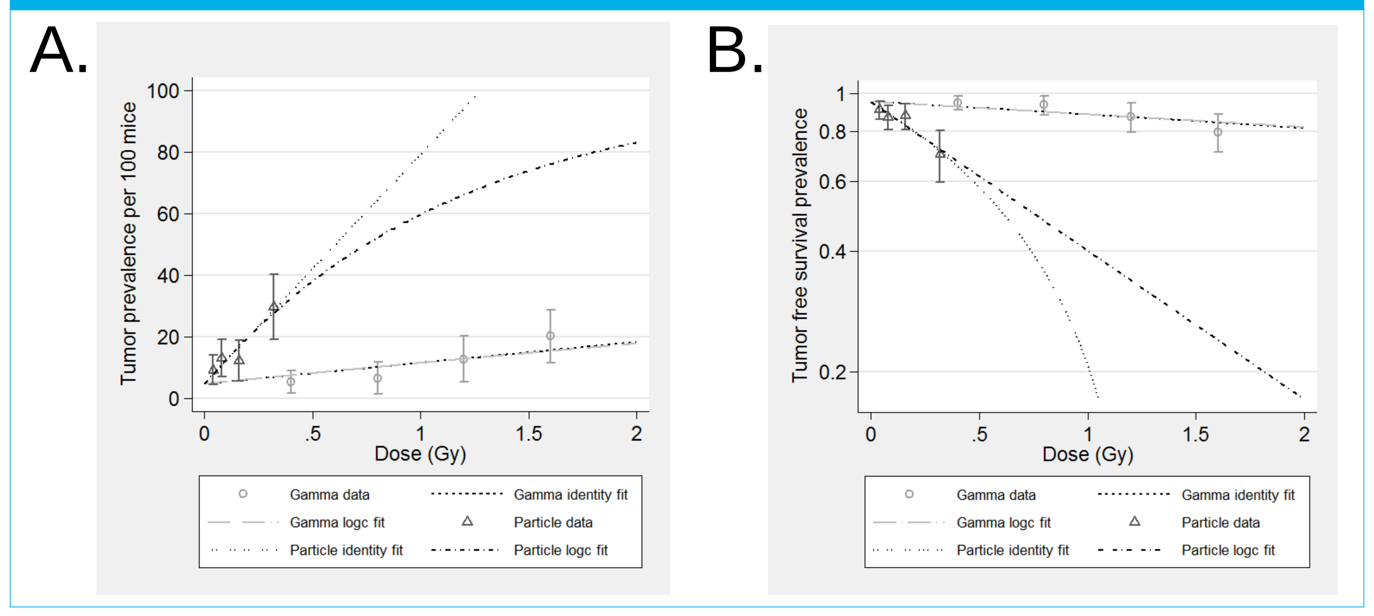
Table 1: Calculating E(D) for Each Combination of Link Function and Effect Scale

	Tumor Prevalence	Log Tumor-Free Survival Prevalence
Identity Function	$E_I(D) = c_{id}+\alpha_{I,id}D$	$E_I(D) = \ln\{1 - (c_{id}+\alpha_{I,id}D)\}$
	$E_\gamma(D) = c_{id}+\alpha_{\gamma,id}D$	$E_\gamma(D) = \ln\{1 - (c_{id}+\alpha_{\gamma,id}D)\}$
Log-complement Function	$E_I(D) = 1 - \exp\{c_{logc}+\alpha_{I,logc}D\}$	$E_I(D) = c_{logc}+\alpha_{I,logc}D$
	$E_\gamma(D) = 1 - \exp\{c_{logc}+\alpha_{\gamma,logc}D\}$	$E_\gamma(D) = c_{logc}+\alpha_{\gamma,logc}D$

Results: Study 1

The background tumor prevalence was 4.8 per 100 mice. The background log tumor-free survival prevalence was -0.05. The link functions fit the data equally well based on Akaike's information criterion.

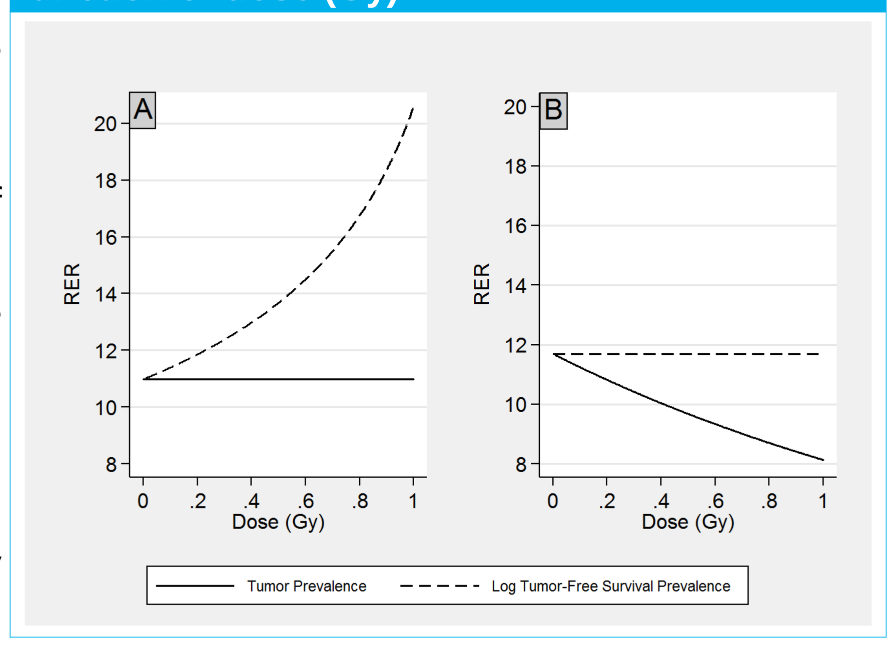
Fig. 1: (A) Harderian gland tumor prevalence and (B) tumor free survival prevalence per 100 mice after exposure to a range of gamma-ray doses and single doses of Si irradiation. Bars represent 95% Wald confidence intervals for the binomial variables.



The RBE values estimated from the identity link and log-complement link are 11.0 (3.2, 17.3) and 11.7 (4.5, 18.9), respectively. The 95% confidence intervals overlap; these differences are not significant. Differences are not seen within link functions over the two effect scales. Therefore, RBE is uniquely defined within models.

Fig. 2 illustrates the RER values estimated from the identity and the log-complement link functions. The RER and RBE are equivalent when both of these models are linear. However, RER estimates change depending on choice of tumor prevalence or log tumor-free survival prevalence effect scale. Thus, RER is not uniquely defined.

Fig. 2: Estimated RER from fitted parameters for (A) the identity function GLM link and (B) the log-complement function GLM link as a function of dose (Gy)



Methods: Study 2

In this study, simulations were run to test the ability of both the RBE and the RER to predict "known" heavy ion effects. The linear equations corresponding to gamma rays and Si from the Chang, et al 2016 [5] data are:

Equation 3: $E_\gamma(D) = 4.8 + 6.8D$

Equation 4: $E_{Si}(D) = 4.8 + 74.4D$

where *E* refers to the effect at any given dose, *D*.

These models were used to predict effects in mice at each gamma ray and Si dose, respectively. For each predicted gamma ray effect, a corresponding Si dose (i.e., the dose of Si required to produce the same gamma ray effect) was back-calculated. The abilities of calculated RBE and RER values from Chang, et al 2016 [5] to predict the original heavy ion data were verified, where original heavy ion data refers to that used to calculate the RBE and RER values. Two data centering schema were used: background Harderian gland tumor level (4.8) and zero [4].

Scale changes are expected when translating effects from mice to humans and between human populations. The data was transformed by subtracting the arbitrary number two from both the gamma ray and Si effects to imitate the change in scale from mouse tumor prevalence to human cancer incidence [5-7]. The response was forced to be zero if the transformation created negative values. The data were also scaled in the opposite direction by adding the arbitrary number fifteen to both the gamma ray and Si effects to model potential human-to-human scaling effects for different disease endpoints, assuming certain populations have higher incidences of certain cancers [8,9]. Additive scaling was used to model both additive risk changes and supra- and sub-multiplicative risk changes, which could require both an additive and a multiplicative component.

Results: Study 2

As both models were linear, RBE was equivalent at all effect values in both the background-centered and zero-centered schema. In the background-centered schema, the RER steadily increased over dose. In the zero-centered schema, the RER was equivalent at all doses and equal to the RBE. Both the back-calculated Si doses from the RBE and the back-calculated Si effects from the RER mapped appropriately to the original doses and effects in both centering schema (not shown).

When the RBE and RER from both the background- and zero-centered schema were applied to the simulated mouse-to-human scaled gamma ray data, the RBE correctly predicted while the RER underpredicted the Si response (Fig. 3).

When the gamma ray and Si data were scaled upwards from their original values (human-to-human scaling simulation), the RBE correctly predicted the Si response in both the background- and zero-centered schema. The RER, on the other hand, overpredicted the Si effect (Fig. 4).

Fig. 3: (A) Background-centered and (B) zero-centered gamma and Si data with RBE and RER effect estimations for potential mouse-to-human predictions

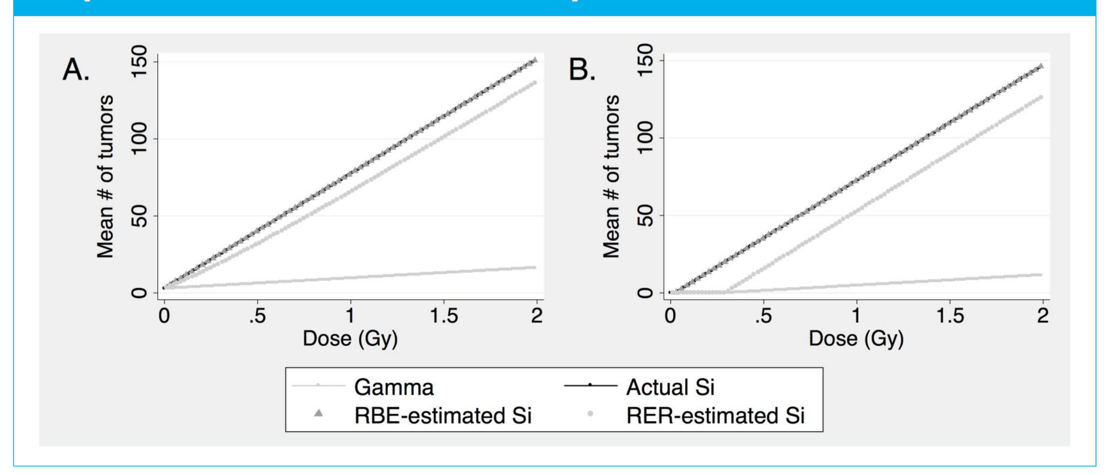
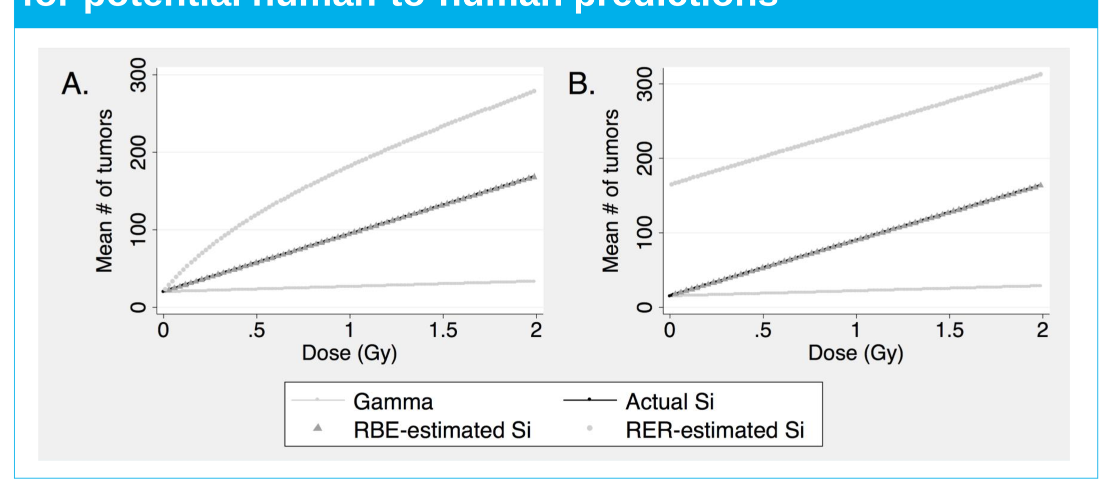


Fig. 4: (A) Background-centered and (B) zero-centered gamma and Si data with RBE and RER effect estimations for potential human-to-human predictions



Conclusions

- RBE was uniquely defined while RER was not
- RBE successfully predicted the scaled Si effects while RER did not
- In this scenario, the dose scale is constant while the effect scale is variable [8,9]
  - RBE depends only on the exposure, while RER depends on the chosen effect
  - The exposure, absorbed dose, is measured identically regardless of the radiation circumstances and target
  - In this context, RBE is predictive of the heavy ion effects while RER is not
- If the effect scale was constant while the dose scale was variable, RER would be uniquely defined while RBE would not be uniquely defined
  - If multiple distinct exposure types were compared in two similar groups of subjects, the effect scale between the two groups would be constant, while the dose scales would be variable
- Given only a single dose-point, an RER could be calculated and applied to later data as an RBE if (and only if) linearity is assumed for both the gamma ray and heavy ion dose responses

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